August 21, 1962

Dr. Seymour Benzer
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Dear Seymour:

Re your paper in the July 1962 Proceedings of the National Academy of Sciences and other notes on suppressors. I have been puzzled a long time by the contradiction in the ideas of easy mutation in code vs. evolutionary stability, and I would reach a slightly different idea than I think you state about suppressors. These do not change any code in a prime sense. They do increase the misreading rate, the imprecision of translation. This will always be selected against, except in the special case of conpensating for a mutant; and the accumulation of suppressors would soon become intolerable. There may be some redundancy of adaptors also, but this cannot lead very far in evolution - or it hasn't. I think Charlie Yanofsky would agree that this view of suppressors also best acoounts for his amino acid substitution findings. A haploid genotype giving a mixture of two proteins does look like some confusion in reading. Whether one can get away with a constant error rate at equivalent sites in all proteins, I am less hopeful than Charlie, and there may be some second order effects on the specificity of the adaptor that concentrate its misreadings in certain contexts. In phage even a very small proportion of normally (incorrectly) read sequences would presumably restore the + phenotype (as does FU).

As ever,

Joshua Lederberg
Professor of Genetics

P.S. I note that Alan has dealt with much the same point. Query: how should we distinguish the interpretation if the "correct" reading is "nonsense"? Can you quantitate the phenotypic effect in r_{II}? Or would the reading hardly be slowed if there were no competing "correct" reading.